이학석사 학위논문

Synthesis of Indoles by Reductive Cyclization of 2-(2-Nitroaryl)acetonitriles in the Presence of Active and Recyclable Co-Rh Heterobimetallic Nanoparticle Catalyst

코발트-로듐 불균일 촉매에 의한 나이트로아릴아세토나이트릴의 환원적 고리화반응을 통한 인돌합성

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최 이 삭

Synthesis of Indoles by Reductive Cyclization of 2-(2-Nitroaryl)acetonitriles in the Presence of Active and Recyclable Co-Rh Heterobimetallic Nanoparticle Catalyst

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이 논문을 이학석사 학위논문으로 제출함

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최이삭의 석사학위논문을 인준함

2017년 2월

위 원 장 _____ (인)

부 위 원 장 _____ (인)

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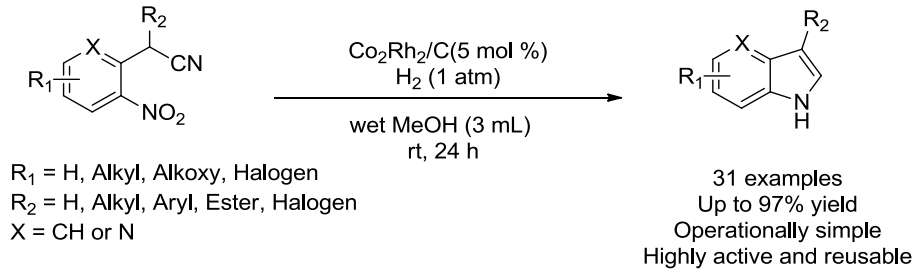
Abstract



A cobalt–rhodium heterobimetallic nanoparticle–catalyzed reductive cyclization of 2–(2–nitroaryl)acetonitriles to indoles has been achieved. The tandem reaction proceeds without any additives under the mild conditions (1 atm H_2 and 25 °C). This procedure could be scaled up to the gram scale. The catalytic system is significantly stable under these reaction conditions and could be reused more than ten times without loss of catalytic activity.

Keywords: heterogeneous catalysis, hydrogenation, reductive cyclization, indoles, azaindoles, tandem reaction, mild condition

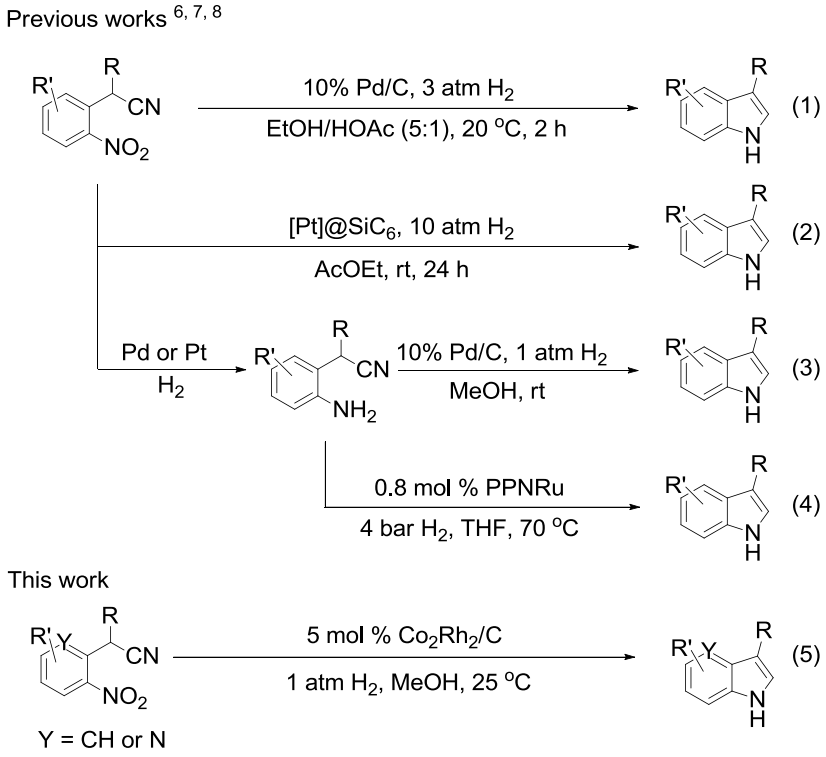
Contents

Introduction

Indoles[1] are ubiquitous structural units of biologically active natural products and pharmaceutical compounds. The synthesis of indoles has attracted substantial attention, and a number of useful synthetic methods for indoles have been developed, established, and reviewed.[2] However, the scope and generality of the synthesis of a particular indole have sometimes been restricted owing to the lack of substrate availability. Consequently, the development of efficient and atom-economical methods for the synthesis of indoles from readily available starting materials is still challenging. From this perspective, 2-(2-nitroaryl)acetonitriles[3] could be good candidates because they are easily obtained from commercially available starting materials and thus might be suitable substrates for the synthesis of 3 to 7-substituted indoles. It has been especially reported[4] that C3-arylindoles exhibit important biological responses. In fact, the use of 2-(2-nitroary1)acetonitriles in the synthesis of indoles has been well-established.[5] For example, Mąkosza reported[6] the reduction of 2-(2-nitroaryl)acetonitriles in the presence of palladium on activated charcoal to the corresponding indoles in moderate to high yields (Scheme 1, eq 1). However, the reaction was very complicated and sensitive to the reaction conditions because the reaction should be carried out in an acidic condition and relatively high pressure where mixture solvent of ethanol and acetic acid (5:1) and 3 atm of hydrogen gas were used together. Nagashima also reported[7] the reaction of 2-

nitrophenylacetonitriles with the heterogeneous platinum catalyst [Pt]@SiC_6 affording a reductive cyclization product, indole, with 52% yield (Scheme 1, eq. 2), but the reaction required 10 atm of hydrogen which is much higher than the pressure used for Mąkosza' s reaction.

Scheme 1. Catalytic synthesis of indoles



Although the use of (2-nitroaryl)acetonitriles as substrates has been revealed as an attractive method for the synthesis of indoles, nevertheless, it has been rarely used for the purpose of indole synthesis in a direct way. Instead, as an indirect way, 2-(2-aminoaryl)acetonitriles, prepared by the reduction of 2-(2-

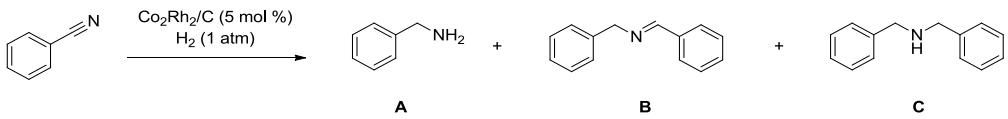
nitroaryl)acetonitriles, has been most commonly used in the conversion to indoles (Scheme1, eq. 3 and eq. 4).[8] Therefore, we were interested in reevaluation for a direct way of use of 2-nitrophenylacetonitriles in the synthesis of indoles by simple hydrogenation.

Recently, the use of heterobimetallic nanoparticles as catalysts has attracted much attention because of their superior catalytic performance compared to that of monometallic nanoparticles.[9] We reported that cobalt/rhodium heterobimetallic nanoparticles (Co_2Rh_2, derived from $Co_2Rh_2(CO)_{12}$) immobilized on charcoal (Co_2Rh_2/C) showed wide usefulness for Pauson-Khand reaction[10] and hydrogenation of nitroarenes.[11] Hoping to find a new catalytic reaction, we found that Co_2Rh_2/C could be used for reductive cyclization of 2-(2-nitroaryl)acetonitriles under atmospheric hydrogen at room temperature, leading to the isolation of indoles with high yields (eq 5). We herein report our results that the reductive cyclization with Co_2Rh_2/C could be conducted under substantially lower pressure, atmospheric hydrogen, and could be reused more than ten times without loss of catalytic activities. As far as we are aware, this is the first report of indoles and azaindoles under only 1 atm of hydrogen at room temperature.

Result and Discussion

Initially, we studied the hydrogenation of benzonitrile under 1 atm of hydrogen (a balloon of hydrogen) at ambient temperature in the presence of Co_2Rh_2/C (Table 1). Benzonitrile was easily converted to benzyl amine, N−benzyl−1−phenylmethanimine, and dibenzyl amine. Because of the high reactivity of Co_2Rh_2/C in the hydrogenation reaction, it was difficult to stop the reaction at the stage of a specific product.

Table 1. Screening data for benzonitriles reduction



A B C

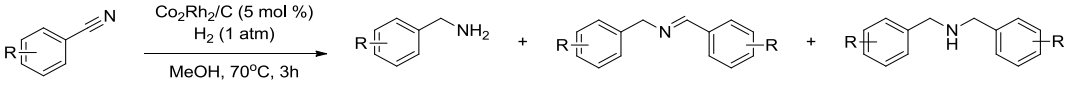
entry	solvent[a]	time (h)	temp (°C)	yield (%)[a] A	B	C
1	*p*−Xylene	18	25	0	4	67
2	EtOH	18	25	0	76	trace
3	MeOH	18	25	0	trace	60
4	*p*−Xylene	3	70	10	17	48
5	EtOH	3	70	5	55	5
6	MeOH	3	70	trace	95	trace

[a]3 mL used. [b]GC yield using mesitylene as internal standard.

However, depending on the arene nitrile substrate itself and reaction conditions, imines or secondary amines could be obtained as

the major product (Table 2). Therefore, we confirmed that nitrile groups could be easily reduced in the presence of a catalytic amount of Co_2Rh_2/C under atmospheric hydrogen. It is notable that the easy formation of secondary amine or imine under mild reaction conditions is remakable.[12]

Table 2. Substrate scopes of various arene nitriles reduction

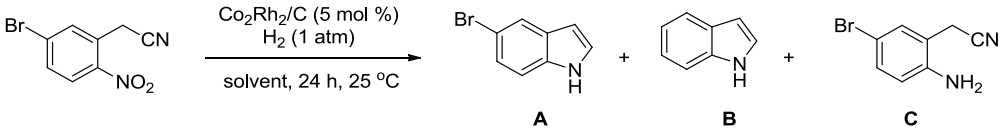


entry	R	conversion (%)	selectivity (%)[a]		
			A	B	C
1	4-Cl	100	8	92	0
2	4-F	83	3	97	0
3	4-OMe	100	4	85	10
4	2-Cl	100	14	66	20

[a] Selectivity detected by GC-Mass.

Encouraged by these observations, we began to investigate the reductive cyclization of 2-(2-nitroaryl)acetonitriles. The reaction conditions were optimized using 0.25 mmol of substrate with 5 mol % Co_2Rh_2/C under 1 atm H_2 (using a balloon of hydrogen) at 25 °C.

Table 3. Screening the reductive cyclization of 2-(5-bromo-2-nitrophenyl)acetonitrile



Entry	Solvent[a]	Time (h)	Cat. (mol %)	Isolated Yield (%) (A / B / C)
1	MeOH	24	5	75 (68 / 7 / 0)
2	THF	24	5	57 (57 / 0 / 0)
3	CH_2Cl_2	24	5	54 (54 / 0 / 0)
4	Benzene	24	5	24 (24 / 0 / 0)
5	Toluene	24	5	57 (57 / 0 / 0)
6	*p*-Xylene	24	5	60 (60 / 0 / 0)
7	MeOH	24	1	62 (10 / 0 / 52)
8	MeOH	24	10	70 (34/ 36 / 0)
9	MeOH	3	5	42 (42 / trace / 0)
10	MeOH	8	5	61 (57/ 4 / 0)
11	MeOH	16	5	69 (62 / 7 / 0)
12	MeOH	24	5	68(63 / 5 / 0)
13	wet MeOH	24	5	76 (70 / 6 / 0)

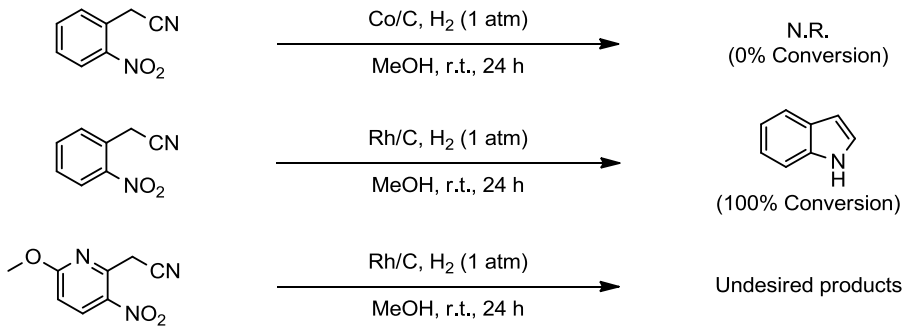
[a]3 mL used. [b]Reaction temperature was 50 °C.

As an initial step, we tried to conduct this reaction with nitrophenyl)acetonitrile, 2-(2-nitrophenyl)propanenitrile, and 2-(2-Nitrophenyl)butanenitrile as a substrate. However, three of corresponding products went through sublimation as dried *in vacuo*,

so that we could not detect an exact yield of each reaction. When we used 2-(5-bromo-2-nitrophenyl)acetonitrile as a substrate, a corresponding product, 5-bromo-1*H*-indole, was isolated without sublimation even after a day during dryness *in vacuo*. With 2-(5-bromo-2-nitrophenyl)acetonitrile as a model substrate, we screened the reaction medium (Table 3, entries 1-6), and reasonable yields were observed for all solvents used. The highest total yield of reductive cyclization products (75%) was observed with methanol, and a debromination product, 1*H*-indole (**B**), was isolated in no more than 7% yield. Using methanol as a representative reaction solvent, we examined how the reaction depended on the amount of Co_2Rh_2/C used (entry 1 *vs* 7 and 8). Decreasing the amount of the catalyst from 5 mol % to 1 mol % led to the formation of a mixture of 5-bromoindole (**A**) and 2-(2-aminophenyl)acetonitrile (**C**) in 10% and 52% yield, respectively (entry 7). When the amount of the catalyst increased from 5 mol % to 10 mol %, formation of **A** and **B** in 34% and 36% yield, respectively, was observed (entry 8). Decreasing the reaction time from 24 h to 3, 8, and 16 h resulted in the isolation of cyclization product in 42%, 61%, and 69% yields, respectively (entries 9-11). When a reaction was conducted at 50 °C, **A** and **B** were isolated in 63% and 5% yields, respectively (entry 12). To our delight, when the reaction was conducted in wet methanol, a similar high yield, 76%, to the reaction conducted in dry methanol was observed (entry 13). This means that the solvent (MeOH) could be used without purification, allowing the catalytic system to be operationally simple.

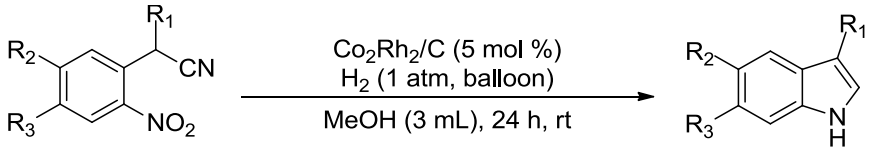
Other metal nanoparticles, such as Co/C and Rh/C, were examined as a catalyst using 2-(2-nitrophenyl)acetonitrile as a substrate (Scheme 2). In a case of Co/C, no reaction was observed. Interestingly, Rh/C showed a high catalytic activity in the reductive cyclization of 2-(2-nitrophenyl)acetonitrile, but no desirable product was obtained in the reaction of 2-(6-methoxy-3-nitropyridin-2-yl)acetonitrile. Among the catalysts studied, no other case gave a higher yield and wider substrate scope than Co_2Rh_2/C. used.

Scheme 2. Reductive Cyclization in the Presence of Monometallic Nanoparticles



Thus, the optimum reaction conditions for the reductive cyclization were temporary established as follows: 0.25 mmol of substrates, 5 mol % Co_2Rh_2/C in 3.0 mL MeOH at 25 °C for a reaction time of 24 h.

Table 4. Synthesis of Indoles[a]



1a - 1α

0.25 mmol

2a - 2α

entry	reactant			yield (%)[a]
	R_1	R_2	R_3	
1	H	H	H	68 (**2a**)
2	Me	H	H	80 (**2b**)
3	Et	H	H	97 (**2c**)
4	Pr	H	H	81 (**2d**)
5	Ph	H	H	83 (**2e**)
6	$4-FC_6H_4$	H	H	86 (**2f**)
7	$4-ClC_6H_4$	H	H	71 (**2g**)
8	$4-MeOC_6H_4$	H	H	78 (**2h**)
9	CH_2Ph	H	H	27 (49)[b] (**2i**)
10	Cl	H	H	56[c] (**2j**)
11	H	F	H	71 (**2k**)
12	H	Cl	H	73 (**2l**)
13	Me	Cl	H	76 (**2m**)
14	Pr	Cl	H	89 (**2n**)
15	H	H	Cl	71 (**2o**)
16	(CO)OEt	H	Cl	91 (**2p**)
17	Me	Br	H	78 (**2q**)
18	Pr	Br	H	53 (**2r**)

19	(CO)OEt	H	Br	92 (**2s**)
20	H	CF_3	H	49 (**2t**)
21	H	H	CF_3	73 (**2u**)
22	H	OMe	H	68 (**2v**)
23	Me	OMe	H	90 (**2w**)
24	Pr	OMe	H	73 (**2x**)
25	H	OMe	OMe	59 (**2y**)
26	2-NO_2-C_6H_4	H	H	79[d] (**2z**)
27	2-(1-nitronaphthalen-2-yl)acetonitrile			77 (**2α**)

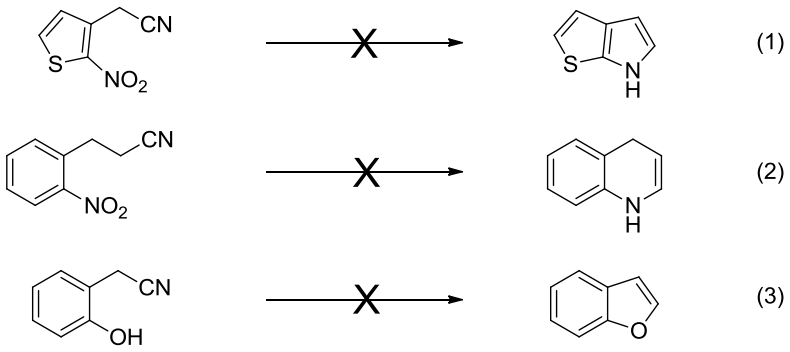
[a] Isolated yield. [b] When the reaction proceeded for 48 h, a yield was 49%. [c] 1*H*-indole was isolated. An isolated product was 2-(1*H*-indol-3-yl)aniline.

With the optimized reaction conditions in hand, the substrate scope of the reaction was next examined (Table 4). The reductive cyclization reaction showed excellent generality for a variety of 2-(2-nitroaryl)acetonitriles substrates. In some cases, sublimation, dehalogenation, and steric hindrance might have a slightly unfavorable effect on the yield. For example, because some indoles suffered from sublimation while drying *in vacuo*, their isolated yields were not as great as we expected. With regard to dehalogenation, bromo-substituted starting materials were merely undergone (entries 17-19). Chloro group at the α position to the nitrile was intolerant likewise under our reaction conditions (entry 10), yielding 1*H*-indole as the sole product. 3-Benzyl-1*H*-indole showed low yield (27%), but this could be overcome and approximately doubled

by lengthening the reaction time (entry 9, 48 h). This result presumably occurred due to the benzyl group, hampering coordination to the nanoparticles as proposed by Sajiki et al.[8a] Beside these observations above, for overall α- substituted 2-(2-nitrophenyl)acetonitrile, the corresponding indoles were isolated in high to excellent yields (71-97%) (entries 2-8). Moreover, the halo (F and Cl) substituents in 2-(5-halo-2-nitrophenyl)aceto-nitriles and 2-(6-halo-2-nitrophenyl)acetonitriles were generally survived (entries 11-16). The corresponding products were isolated in reasonable to high yields (71-91%). In general, both electron-donating (OMe) and withdrawing (F, Cl, Br, CF_3) groups on the aromatic substituents of the substrates are tolerated (entries 11-25). When 2,2-bis(2-nitrophenyl)acetonitrile was used as a substrate, 2-(1*H*-indol-3-yl)aniline, widely used in the synthesis of indolo[2,3-c]quinolines,[13] was isolated in 79% yield (entry 26). Treatment of 2-(1-nitronaphthalen-2-yl)acetonitrile with hydrogen afforded 1*H*-benzo[g]indole in 77% yield. This presents the first synthesis of 1*H*-benzo[g]indole from the substrate having both a nitrile and a nitro group via the reductive cyclization (entry 27). In addition, we tested several modified versions of this reaction under the optimized condition (Scheme 3). Thiophene derivatives could not show a cyclized product, 6*H*-thieno[2,3-b]pyrrole (Scheme 3, eq 1). Also, we expected that relatively remote positioned nitriles could be attacked by amines reduced from nitro group, which producing 1,4-dihydroquinoline, but we could not isolated the desired product (Scheme 3, eq 2). Lastly, we

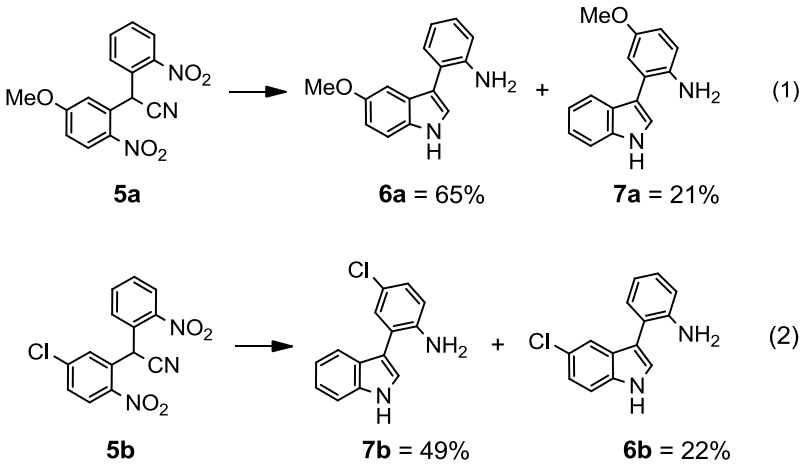
anticipated that hydroxyl group could attack nitrile group followed by removal of NH_3, making benzofuran, but unfortunately, we could not obtain the expected product (Scheme 3, eq 3).

Scheme 3. Modified version of this reaction



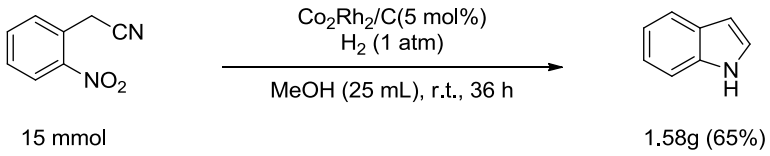
To test electronic effects, (5−methoxy−2−nitrophenyl)−2−(2−nitrophenyl)acetonitrile and 2−(5−chloro−2−nitrophenyl)−2−(2−nitrophenyl)acetonitrile, were prepared and reacted under our reaction conditions (Scheme 4). Notably, an aromatic group with an electron−donating group (OMe) gave three times more cyclization product than an aromatic group without a methoxy group. In the first reaction, 2−(5−methoxy−1*H*−indol−3−yl)aniline and 2−(1*H*−indol−3−yl)−4−methoxyaniline were isolated in 65% and 21% yield, respectively. In the second reaction, 2−(5−chloro−1*H*−indol−3−yl)aniline, and 4−chloro−2−(1*H*−indol−3−yl)aniline were isolated in 22% and 49% yields, respectively. This observation clearly demonstrated that the electron−richness of substituent favors the intramolecular nucleophilic attack of the amine group, helping cyclization.

Scheme 4. Competition experiments



In addition, the reaction could be conducted on a gram-scale (Scheme 5). 1.58 g of 1*H*-indole, was isolated in 65% yield from 2-(2-nitrophenyl)acetonitrile. Thus, it was proved that scale-up of the procedure resulted in no reduction in the yield.

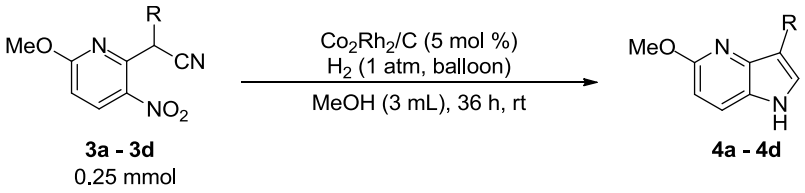
Scheme 5. Gram-scale experiment



Azaindoles possess remarkable pharmacological and physicochemical properties, although their direct functionalization at the C3 position is not straightforward.[14] Thus, we investigated the reductive cyclization of 2-(3-nitropyridin-2-yl)acetonitrile derivatives under our mild conditions (Table 5). Pyridine derivatives were then hydrogenated to provide the corresponding C3-

substituted 4-azaindoles in high yields (61-72%).

Table 5. Synthesis of Azaindoles



3a - 3d
0.25 mmol

4a - 4d

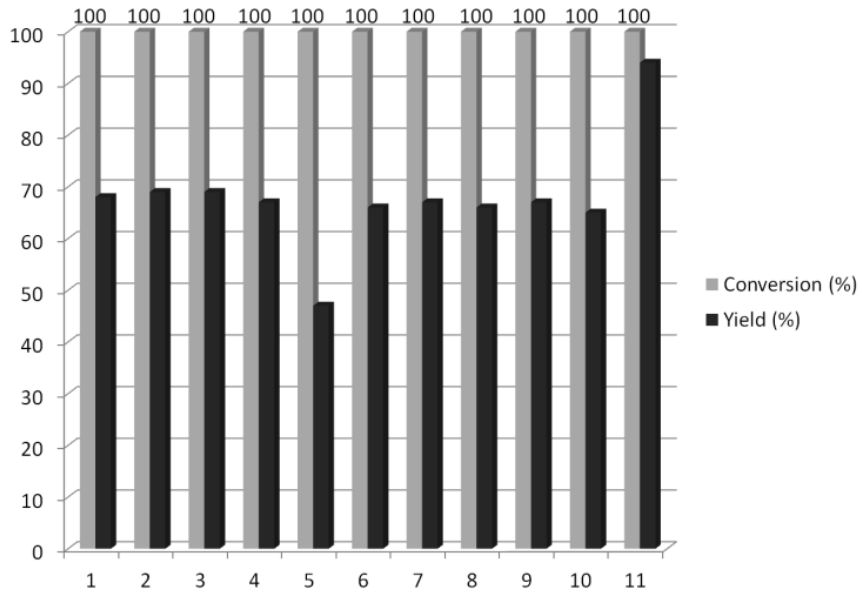
entry	Reactant	isolated yield (%)[a]
1	R = H	61 (**4a**)
2	R = Me	72 (**4b**)
3	R = Pr	67 (**4c**)
4	R = $CH_2(CO)OEt$	65 (**4d**)

Thus, the catalytic reaction process developed in this study revealed a greatly easy and simple way to make both indoles and azaindoles under the user-friendly condition (1 atm H_2 and 25 °C).

Recyclability is one of the strong points for heterogeneous catalysts. Therefore, the reusability of Co_2Rh_2/C was examined for the reductive cyclization of 2-(2-nitrophenyl)acetonitrile (Figure 1). After each reaction, the catalyst was separated from the reaction mixture by centrifuge, dried in vacuum, and then reused for the further catalytic reactions. For ten runs, 68%, 69%, 69%, 67%, 47%, 66%, 67%, 66%, 67%, and 65%, yields were shown respectively. The conversion rate for each cycle was almost quantitative, but the isolated yield for each cycle was not particularly high due to the sublimation effect as mentioned above. According to the GC-Mass analysis of the reaction products, no major byproducts were formed

except a trace amount of 2-(2-aminophenyl)acetonitrile. Strangely, at the fifth cycle, the formation of 2-(2-aminophenyl)acetonitrile (10%) was observed; however, the catalytic activity was restored in the subsequent cycle. This suggested an experimental error at the fifth cycle. The reductive cyclization of 2-(2-nitrophenyl)butanenitrile under the same reaction conditions was also tested as below after the ten runs, showing that the catalyst was still highly stable with other substrates under our reaction conditions. Therefore, the catalytic system showed a great capability of reuse and a significant air-stability under the reaction conditions.

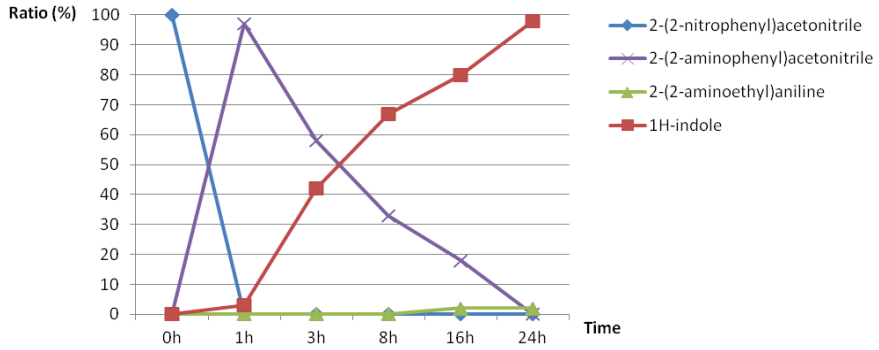
Figure 1. Reuse of Co_2Rh_2/C in the Synthesis of Indoles



To obtain an insight on the reaction mechanism, we monitored the reaction intermediate generated in the reductive cyclization of 2-

(2−nitrophenyl)acetonitrile by GC−Mass (Figure 2). Initially, rapid consumption of 2−(2−nitrophenyl)acetonitrile (blue line) along with the formation of 2−(2−aminophenyl)acetonitrile (purple line) was observed. As time passed, the concentration of 1*H*−indole (red line) increased and that of 2−(2−aminophenyl)acetonitrile decreased. At the later stage, the formation of 2−(2−aminoethyl)aniline (green line) was observed and slowly increased; however, its amount was negligible.

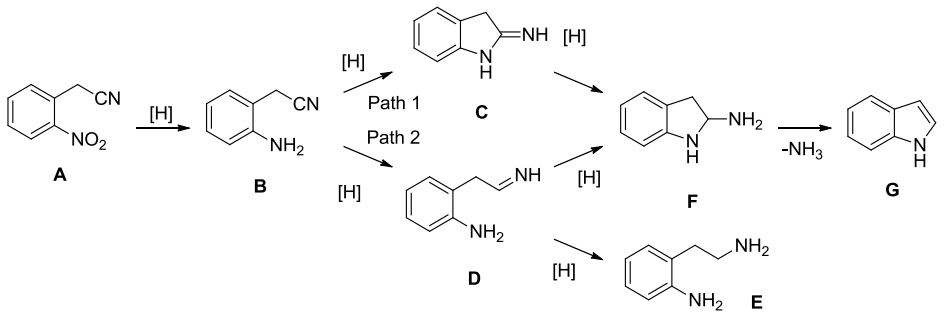
Figure 2. Monitoring the synthesis of 1*H*−indole from 2−(2−nitrophenyl)acetonitrile



Based on these results, plausible reaction pathways were proposed (Scheme 6). Although we failed to detect the intermediate amidine or imine, two pathways could be proposed. Pathway 1 included the nucleophilic attack of amine on the nitrile carbon, resulting in the formation of amidine (**C**). Nitriles were presumably activated by the coordination of Co−Rh heterobimetallic nanoparticle as proposed by Sajiki et al.[8] Pathway 2 proceeded via an imine intermediate (**D**). According to our study on the nitrile reduction, nitriles in MeOH

were easily reduced to an imine at room temperature in the presence of Co_2Rh_2/C. Thus, the generated imine intermediate could be readily attacked by an amine to form a cyclized intermediate (F). This pathway could also lead to the formation of 2-(2-aminoethyl)aniline (E) detected during the GC-Mass monitoring.

Scheme 6. Proposed Reaction Pathway



Conclusion

We have developed an operationally simple, highly active, and recyclable method for the Co_2Rh_2 nanoparticles/charcoal-catalyzed cascade reductive cyclization of (2-nitroaryl)acetonitriles to indoles and 2-(3-nitropyridin-2-yl)acetonitrile to azaindoles within 24 h. To the best of our knowledge, this is the first report of indoles and azaindoles synthesis under only 1 atm of hydrogen at room temperature. Advantageously, no complicated ligands or additional acid or base is needed. The experimental simplicity and reusability (more than ten times) are especially attractive features of the catalytic system and should encourage its use among synthetic chemists. Further investigations of the present catalytic system for other reactions are currently ongoing in our laboratory.

Experimental Section

1. General Remarks

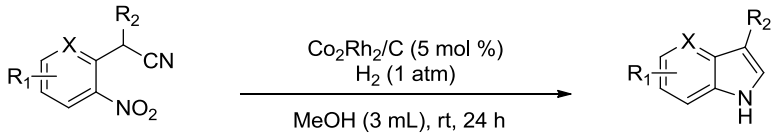
Workup procedures were done in air. All solvents were used without further purification. Unless otherwise noted, all commercial materials were used without purification. Reagents were purchased from Sigma-Aldrich, Alfa Aesar, Acros, and TCI and were used as received. High purity H_2 (99.999%) was used. TLC analysis of reaction mixtures was performed on Merck silica gel 60 F254 TLC plates. TLC plates were visualized by ultraviolet light and treated with acidic *p*-anisaldehyde stain followed by gentle heating. Flash column chromatography was carried out on Merck 60 silica gel (230-400 mesh). ^{1}H NMR, ^{13}C NMR, ^{19}F NMR spectra were recorded with Agilent 400-MR DD2 (400 MHz, 100 MHz, and 376 MHz respectively) and ^{1}H NMR, ^{13}C NMR spectra were recorded with Varian (500 MHz and 125 MHz, respectively) spectrometer. ^{1}H NMR spectra were taken in $CDCl_3$ and were referenced to residual TMS (0 ppm) and reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d= doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), and integration. Chemical shifts of the ^{13}C NMR spectra were measured relative to $CDCl_3$ (77.16 ppm) and DMSO-d_6 (39.52 ppm). High-Resolution Mass Spectra were obtained at the Korea Basic Science Institute (Daegu, South Korea) on a Jeol JMS 700 high resolution mass spectrometer. **1a**, **1u**, **1y**, and **3a** are commercially available compounds.

2. Immobilization of Co/Rh Nanoparticles on Charcoal [15]

To a two-neck flask were added *o*-dichlorobenzene (10 mL), oleic acid (0.2 mL), and trioctylphosphine oxide (0.4 g). While the solution was heated at 180 °C, a solution of metal carbonyl $Co_2Rh_2(CO)_{12}$ (0.8 g) in 25 ml *o*-dichlorobenzene was injected into the flask. The resulting solution was heated to 180 °C for 2 h and then concentrated to a volume of 5 mL. The concentrated solution was cooled to room temperature. To the cooled solution was added 30 mL of THF. After the solution was well stirred for 10 min, flame-dried charcoal (1.6 g) was added to the solution. After the resulting solution had been refluxed for 12 h, the precipitates were filtered and washed with diethyl ether (20 mL), dichloromethane (20 mL), acetone (20 mL), and methanol (20 mL). Vacuum drying gave a black solid.

3. Experimental Procedures

A. General procedure 1: Synthesis of indoles catalyzed by Co_2Rh_2/C

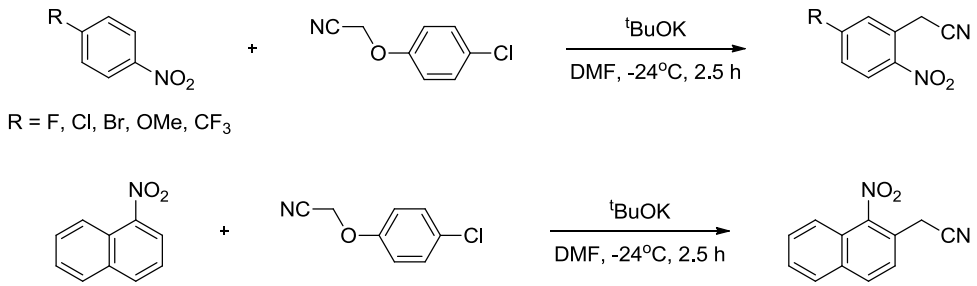


R_1 = H, Alkyl, Alkoxy, Halogen
R_2 = H, Alkyl, Aryl, Halogen
X = CH orN

Reactions were performed in a tube-type schlenk flask equipped with a stirring bar and capped with a rubber septum. The followings were placed in the flask in order: a substrate (0.25 mmol), 5 mol% of Co_2Rh_2 (90 mg of the immobilized Co_2Rh_2/C)[16], and methanol (3

mL). The solution was bubbled by hydrogen gas for 1 hour. The solution was stirred for 24 h and then was filtered and concentrated by a rotary evaporator. The product was purified by chromatography on a silica gel column eluting with either hexane/ethyl acetate (10:1) or pentane/ether (5:1) according to the compounds' R_f values. Products were characterized by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and HRMS. Isolated yields: 49 to 97% depending on substrates and conditions.

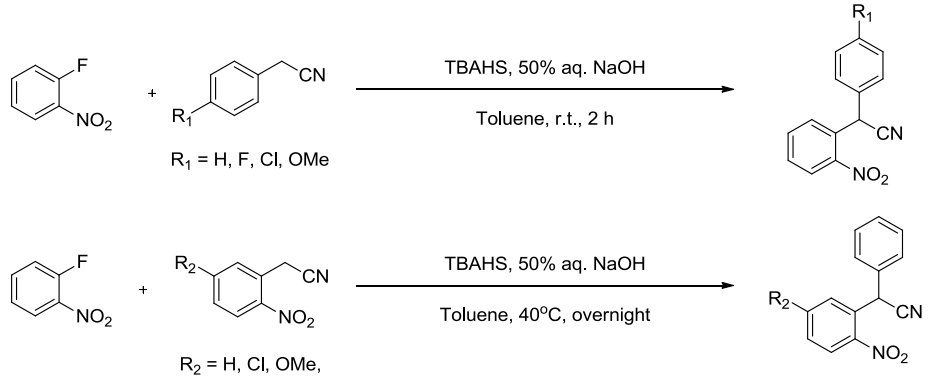
B. General Procedure 2: Vicarious nucleophilic aromatic substitution[17] (**1k**, **1l**, **1t**, **1v**, and **1*α***)



A solution of 10 mmol of an aromatic nitro compound and 1.2 equiv of 4-chlorophenoxyacetonitrile in anhydrous DMF (10 mL) was added dropwise to a solution of 2.3 equivalents of potassium *tert*-butoxide in DMF (15 mL) at −24 °C. The color of the reaction mixture was turned to deep purple very soon, and the mixture was stirred at −24 °C for 2.5 h. After reaction, the reaction mixture was transferred into 200 mL of ice cold 5 % HCl. The solution was directly extracted with ethyl acetate and the extracts were purified by flash chromatography on a silica gel column eluting with

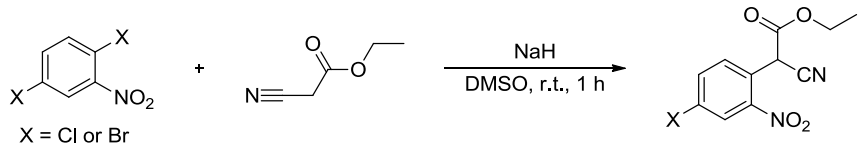
petroleum ether/ethyl acetate (15:1). Isolated yields: 55 to 61% depending on reactants and conditions.

C. General Procedure 3: Nucleophilic aromatic substitution[18] (1e, 1f, 1g, 1h, and 1z)



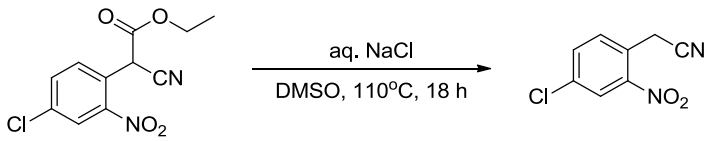
To a one-neck schlenk were added 1-fluoro-2-nitrobenzene (5 mmol), 1 equiv of phenylacetonitrile, 1 equiv of tetrabutyl-ammonium hydrogensulfate (TBAHS) and 50% aqueous NaOH solution (2 mL) with distilled toluene (15 mL). The reaction mixture was reacted under the specified temperature and time. The mixture was poured into 3 M HCl. The mixture was then stirred at 20 °C for 30 min and then the organic layer was separated with diethyl ether. The ether solution was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*, and the residue was purified by flash column chromatography on a silica gel column eluting with hexane/ethyl acetate (25:1). Isolated yields: 52 to 68% depending on reactants and conditions.

D. General procedure 4[19] (1p and 1s)



To 1 equiv of ethyl cyanoacetate in 10 mL of anhydrous DMSO was added 1 equiv of sodium hydride in 5 mL of anhydrous DMSO. After the solution was stirred for 10 min, 1,4-dichloro-2-nitrobenzene or 1,4-dibromo-2-nitrobenzene (10 mmol) was added. The reaction mixture was stirred at room temperature for 1 h. After the solution was quenched with water, the organic layer was extracted with dichloromethane. The CH_2Cl_2 solution was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*, and the residue was purified by flash column chromatography on a silica gel column eluting with petroleum ether/ethyl acetate (10:1). Isolated yields: 71 to 73% depending on reactants and conditions.

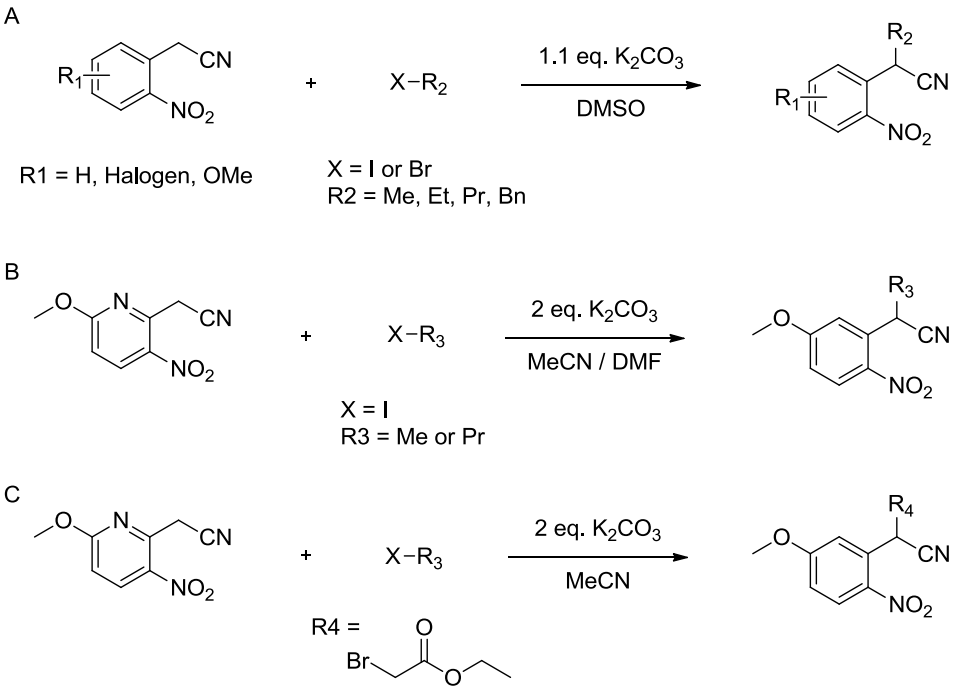
E. General procedure 5 (1o)



To 5 mmol of ester in DMSO was added brine (prepared by dissolving 1.5 equivalent of NaCl in water). The reaction mixture was stirred at 110 °C for 18 h. The mixture was allowed to cool down to 20 °C, then was diluted with ethyl acetate. The organic solution was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*, and the residue was purified by flash column

chromatography on a silica gel column eluting with petroleum ether/ethyl acetate (2:1). Isolated yields: 99%

F. General procedure 6: Direct alkylation [20, 21] (1b, 1c, 1d, 1i, 1m, 1n, 1q, 1r, 1w, 1x, 3b, 3c, and 3d)



A 10 mmol of substrate was dissolved in a proper solvent as shown above. 1.1 equiv of potassium carbonate was added to the solution and the resulting solution was stirred for 20 min. 1.1 Equiv of a corresponding alkyl halide was slowly added. After the solution was stirred for a few hours, the resulting solution was quenched with water and the organic layer was extracted with dichloromethane. The organic solution was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*, and the residue was purified by flash column chromatography on a silica gel column eluting with petroleum

ether/ethyl acetate (20:1). Isolated yields: 51 to 99% depending on reactants and conditions.

G. General procedure 7[22] (1j)

To a stirred solution of benzaldehyde (10 mmol) and sodium cyanide (10 mmol) in water (20 mL) at 0° C was added sodium bisulfite (10 mmol). The reaction mixture was stirred at room temperature for 6 h. The product was extracted with benzene and the extracts were washed successively with H_2O and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford 2-hydroxy-2-phenylacetonitrile. Without purification, a solution of 2-hydroxy-2-phenylacetonitrile (7 mmol) was added to a stirred solution of pyridine (14 mmol) and phosphorus oxychloride (8.4 mmol) in anhydrous benzene (20 mL) at room temperature. The reaction mixture was stirred at the same temperature for overnight and the solvent was evaporated *in vacuo.* The residue was diluted with diethyl ether and water. Removal of the solvent, followed by chromatography eluting with hexane/ethyl acetate (20:1) gave a corresponding product. Overall yield: 62%

4. Characterization Data for Isolated Products

2-(5-Bromo-2-nitrophenyl)acetonitrile (Table 1)

Yellow solid (1.37g, 57%); m. p. 106.7 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (d, J = 8.7 Hz, 1 H), 7.96 (s, 1 H), 7.88 (d, J = 8.7 Hz, 1 H), 4.32 (s, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.85, 134.46, 132.67, 128.73, 128.03, 127.43, 117.45, 40.15, 39.94, 39.73, 39.52, 39.31, 39.10, 38.89, 21.39; HRMS (EI$^+$): m/z calcd for $[C_8H_5BrN_2O_2]^+$: 239.9534, found 239.9535.

2-(2-Nitrophenyl)propanenitrile (Table 2, Entry 2, **1b**)

Yellow solid (1.72g, 98%); m. p. 43.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.1 Hz, 1 H), 7.78 (d, J = 7.8 Hz, 1 H), 7.69 (t, J = 7.5 Hz, 1 H), 7.50 (t, J = 7.7 Hz, 1 H), 4.79-4.61 (m, 1 H), 1.69 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 223.91, 147.47, 134.37, 132.30, 129.69, 129.41, 125.61, 120.76, 77.42, 77.16, 76.91, 28.10, 21.21; HRMS (EI$^+$): m/z calcd for $[C_9H_8N_2O_2]^+$: 177.0664, found 177.0662.

2-(2-Nitrophenyl)butanenitrile (Table 2, Entry 3, **1c**)

Yellow liquid (1.80g, 95%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.1 Hz, 1 H), 7.75-7.61 (m, 2 H), 7.48 (t, J = 7.6 Hz, 1 H), 4.59

(dd, J = 8.7, 4.9 Hz, 1 H), 2.09−1.78 (m, 2 H), 1.11 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.44, 133.86, 130.79, 129.89, 129.12, 125.34, 119.69, 35.02, 28.61, 11.53; HRMS (EI^+): m/z calcd for $[C_{10}H_{10}N_2O_2]^+$: 191.0821, found 191.0824.

2−(2−Nitrophenyl)pentanenitrile (Table 2, Entry 4, **1d**)

Yellow liquid (1.98g, 97%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.2 Hz, 1 H), 7.73 (d, J = 7.7 Hz, 1 H), 7.66 (t, J = 7.6 Hz, 1 H), 7.48 (t, J = 7.7 Hz, 1 H), 4.81−4.53 (m, 1 H), 1.99−1.74 (m, 3 H), 1.70−1.46 (m, J = 15.0, 7.4 Hz, 3H), 0.95 (t, J = 7.3 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.33, 133.87, 131.08, 129.84, 129.03, 125.27, 119.77, 37.04, 33.26, 20.39, 12.94; HRMS (EI^+): m/z calcd for $[C_{11}H_{12}N_2O_2]^+$: 205.0977, found 205.0979.

2−(2−Nitrophenyl)−2−phenylacetronitrile (Table 2, Entry 5, **1e**)

Yellow oil (0.75g, 63%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.0 Hz, 1 H), 7.63−7.52 (m, 2 H), 7.45−7.37 (m, 1 H), 7.30−7.16 (m, 5 H), 6.04 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.65, 134.20, 134.11, 130.96, 130.48, 129.75, 129.32, 128.70, 127.89, 125.77, 118.68, 77.48, 77.16, 76.84, 38.33; HRMS (EI^+): m/z calcd for $[C_{14}H_{10}N_2O_2]^+$: 239.0821, found 239.0824.

2-(4-fluorophenyl)-2-(2-nitrophenyl)acetonitrile (Table 2, Entry 6, **1f**)

Yellow oil (0.79g, 62%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, J = 8.1 Hz, 1 H), 7.62 (qd, J = 7.8, 1.3 Hz, 2 H), 7.48-7.43 (m, 1 H), 7.24-7.17 (m, 2 H), 6.97-6.90 (m, 2 H), 6.04 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.63, 161.65, 147.60, 134.33, 130.85, 130.30, 130.06, 130.04, 129.94, 129.82, 129.75, 125.92, 118.55, 116.44, 116.26, 77.42, 77.16, 76.91, 37.78; ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.51, -112.52, -112.53, -112.55, -112.56, -112.57, -112.58; HRMS (EI^+): m/z calcd for $[C_{14}H_9FN_2O_2]^+$: 257.0726, found 257.0729.

2-(4-Chlorophenyl)-2-(2-nitrophenyl)acetonitrile (Table 2, Entry 7, **1g**)

Yellow oil (0.70g, 52%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 8.2 Hz, 1 H), 7.57-7.48 (m, 2 H), 7.39-7.32 (m, 1 H), 7.16-7.07 (m, 4 H), 5.96 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.29, 134.41, 134.21, 132.63, 130.74, 129.81, 129.70, 129.21, 129.12, 125.70, 118.21, 77.42, 77.16, 76.90, 37.75; HRMS (EI^+): m/z calcd for $[C_{14}H_9ClN_2O_2]^+$: 273.0431, found 273.0428.

2-(4-Methoxyphenyl)-2-(2-nitrophenyl)acetonitrile (Table 2, Entry 8, **1h**)

Yellow oil (0.91g, 68%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, J = 8.1 Hz, 1 H), 7.66 (d, J = 7.8 Hz, 1 H), 7.61 (t, J = 7.6 Hz, 1 H), 7.45 (t, J = 7.7 Hz, 1 H), 7.14 (d, J = 8.6 Hz, 2 H), 6.79 (d, J = 8.4 Hz, 2 H), 6.02 (s, 1 H), 3.70 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.85, 147.75, 134.21, 131.04, 130.85, 129.69, 129.25, 126.13, 125.88, 118.97, 114.79, 77.48, 77.16, 76.84, 55.44, 37.77; HRMS (EI^+): m/z calcd for $[C_{15}H_{12}N_2O_3]^+$: 269.0926, found 269.0928

2-(2-Nitrophenyl)-3-phenylpropanenitrile (Table 2, Entry 9, **1i**)

White solid (2.24g, 89%); m. p. 94.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (m, 1 H), 7.63 (s, 2 H), 7.48 (m, 1 H), 7.23 (m, 5 H), 4.94-4.85 (m, 1 H), 3.25 (d, J = 13.4 Hz, 1 H), 3.03 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.63, 135.68, 134.22, 130.64, 129.62, 129.43, 128.91, 127.84, 125.78, 119.65, 77.48, 77.16, 76.84, 41.51, 36.60; HRMS (EI^+): m/z calcd for $[C_{15}H_{12}N_2O_2]^+$: 253.0977, found 253.0975.

2-Chloro-2-(2-nitrophenyl)acetonitrile (Table 2, Entry 10, **1j**)

White solid (1.21g, 62%); m. p. 52.9 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, J = 7.8 Hz, 1 H), 7.97 (d, J = 7.9 Hz, 1 H), 7.75 (t, J = 7.8 Hz, 1 H), 7.62 (t, J = 7.8 Hz, 1 H), 6.52 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.57, 134.87, 131.82, 130.54, 128.10, 126.17,

115.34, 77.41, 77.16, 76.91, 40.36; HRMS (EI^+): m/z calcd for $[C_8H_5ClN_2O_2]^+$: 196.0040, found 196.0037.

2-(5-Fluoro-2-nitrophenyl)acetonitrile (Table 2, Entry 11, **1k**)

Yellow solid (0.99g, 55%); m. p. 71.1 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25-8.17 (m, 1 H), 7.44-7.36 (m, 1 H), 7.22-7.13 (m, 1 H), 4.18 (s, 2 H), 4.18 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.63, 164.04, 143.67, 129.48, 129.39, 129.04, 128.94, 128.90, 118.61, 118.35, 116.84, 116.61, 115.93, 77.48, 77.16, 76.84, 23.12; ^{19}F NMR (376 MHz, $cdcl_3$) δ -100.29, -100.31, -100.33, -100.34; HRMS (EI^+): m/z calcd for $[C_8H_5FN_2O_2]^+$: 180.0335, found 180.0337.

2-(5-Chloro-2-nitrophenyl)acetonitrile (Table 2, Entry 12, **1l**)

Yellow solid (1.21g, 62%); m. p. 92.9 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 8.21 (d, J = 8.8 Hz, 1 H), 7.84 (d, J = 2.1 Hz, 1 H), 7.76 (dd, J = 8.8, 2.2 Hz, 1 H), 4.35 (s, 2 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 146.39, 138.97, 131.53, 129.63, 128.75, 127.46, 117.39, 40.02, 39.85, 39.69, 39.52, 39.35, 39.19, 39.02, 21.51; HRMS (EI^+): m/z calcd for $[C_8H_5ClN_2O_2]^+$:196.0040, found 196.0043.

2-(5-Chloro-2-nitrophenyl)propanenitrile (Table 2, Entry 13, **1m**)

White solid (1.91g, 91%); m. p. 95.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.8 Hz, 1 H), 7.71 (d, J = 1.4 Hz, 1 H), 7.43 (dd, J = 8.8, 1.4 Hz, 1 H), 4.72 (q, J = 7.1 Hz, 1 H), 1.66 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.68, 141.13, 134.40, 129.93, 129.73, 127.33, 120.23, 77.48, 77.16, 76.84, 28.19, 21.17; HRMS (EI^+): m/z calcd for $[C_9H_7ClN_2O_2]^+$: 210.0196, found 210.0198.

2-(5-Chloro-2-nitrophenyl)pentanenitrile (Table 2, Entry 14, **1n**)

Yellow oil (2.07g, 87%); ^{1}H NMR (400 MHz, $cdcl_3$) δ 7.96 (d, J = 8.8 Hz, 1 H), 7.69 (d, J = 2.0 Hz, 1 H), 7.42 (dd, J = 8.8, 2.0 Hz, 1 H), 4.67 (dd, J = 8.4, 6.0 Hz, 1 H), 1.92-1.72 (m, 2 H), 1.68-1.42 (m, 2 H), 0.94 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.72, 140.88, 133.55, 130.26, 129.56, 127.29, 119.52, 77.48, 77.16, 76.84, 37.42, 33.68, 20.79, 13.28; HRMS (EI^+): m/z calcd for $[C_{11}H_{11}ClN_2O_2]^+$: 239.0587, found 239.0589.

2-(4-Chloro-2-nitrophenyl)acetonitrile (Table 2, Entry 15, **1o**)

Yellow solid (0.97g, 99%); m. p. 86.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1 H), 7.63 (s, 2 H), 4.11 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.87, 135.75, 134.56, 132.35, 126.09, 124.31, 116.05,

77.48, 77.16, 76.84, 22.49; HRMS (EI+): m/z calcd for $[C_8H_5ClN_2O_2]^+$: 196.0040, found 196.0038.

Ethyl 2-(4-chloro-2-nitrophenyl)-2-cyanoacetate (Table 2, Entry 16, **1p**)

Yellow oil (1.90g, 71%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20-8.02 (m, 1 H), 7.72-7.55 (m, 2 H), 5.61-5.43 (m, 1 H), 4.34-4.10 (m, 2 H), 1.34-1.16 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.18, 147.66, 136.63, 134.44, 132.63, 126.22, 123.76, 114.12, 77.36, 77.11, 76.85, 64.07, 40.86, 13.83; HRMS (EI^+): m/z calcd for $[C_{11}H_9ClN_2O_4]^+$: 197.1204, found 197.1205; HRMS (EI+): m/z calcd for $[C_{18}H_{17}NO]^+$: 269.0329, found 2690331; IR (neat): 1751cm^{-1}.

2-(5-Bromo-2-nitrophenyl)propanenitrile (Table 2, Entry 17, **1q**)

Yellow solid (2.42g, 95%); m. p. 94.7 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.02 (d, J = 8.7 Hz, 2 H), 7.87 (d, J = 8.7 Hz, 1 H), 4.75 (q, J = 7.1 Hz, 1 H), 1.67 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 146.85, 133.96, 132.58, 132.41, 127.90, 127.27, 120.87, 40.02, 39.86, 39.69, 39.52, 39.35, 39.19, 39.02, 27.14, 19.30; HRMS (EI^+): m/z calcd for $[C_9H_7BrN_2O_2]^+$: 253.9691, found 253.9693.

2-(5-Bromo-2-nitrophenyl)pantanenitrile (Table 2, Entry 18, **1r**)

Yellow solid (2.60g, 92%); m. p. 54.6 °C; ^{1}H NMR (500 MHz, DMSO−d_6) δ 8.08−7.93 (m, 2 H), 7.87 (d, J = 8.7 Hz, 1 H), 4.67 (dd, J = 9.9, 5.1 Hz, 1 H), 2.09−1.82 (m, 2 H), 1.59−1.38 (m, 2 H), 0.95 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO−d_6) δ 146.91, 133.00, 132.76, 132.59, 127.78, 127.38, 120.03, 40.02, 39.86, 39.69, 39.52, 39.35, 39.19, 39.02, 35.31, 32.69, 20.24, 13.05; HRMS (EI$^+$): m/z calcd for $[C_{11}H_{11}BrN_2O_2]^+$: 282.0004, found 282.0002.

Ethyl 2−(4−bromo−2−nitrophenyl)−2−cyanoacetate (Table 2, Entry 19, **1s**)

Red solid (2.28g, 73%); m. p. 66.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30−8.22 (m, 1 H), 7.81 (d, J = 8.3 Hz, 1 H), 7.58 (d, J = 8.3 Hz, 1 H), 5.55 (s, 1 H), 4.23 (q, J = 7.1 Hz, 2 H), 1.25 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.17, 147.80, 137.53, 132.78, 129.20, 124.30, 124.28, 114.14, 77.41, 77.16, 76.90, 64.24, 41.02, 13.98; HRMS (EI$^+$): m/z calcd for $[C_{11}H_9BrN_2O_4]^+$: 312.9824, found 312.9820; IR (neat): 1750cm^{-1}.

2−(2−Nitro−5−(trifluoromethyl)phenyl)acetonitrile (Table 2, Entry 20, **1t**)

Yellow solid (1.35g, 59%); m. p. 57.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ δ 8.25−8.15 (m, J = 8.2, 4.4 Hz, 1H), 7.90 (s, 1H), 7.83−7.72 (m, J = 7.9 Hz, 1H), 4.16 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ^{13}C

NMR (125 MHz, $CDCl_3$) δ 149.65, 136.36, 136.09, 135.82, 135.55, 128.60, 128.57, 127.06, 127.03, 126.98, 126.59, 123.64, 121.47, 115.62, 77.41, 77.16, 76.91, 22.69; ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.32; HRMS (EI^+): m/z calcd for $[C_9H_5F_3N_2O_2]^+$: 179.1310, found 179.1313.

2-(5-Methoxy-2-nitrophenyl)acetonitrile (Table 2, Entry 22, **1v**)

Yellow solid (1.17g, 61%); m. p. 81.2 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 8.22 (d, J = 9.1 Hz, 1 H), 7.25 (d, J = 2.4 Hz, 1 H), 7.17 (dd, J = 9.1, 2.6 Hz, 1 H), 4.33 (s, 2 H), 3.92 (s, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.48, 140.43, 129.45, 128.31, 117.75, 117.30, 114.06, 56.31, 40.02, 39.86, 39.69, 39.52, 39.35, 39.19, 39.02, 22.31; HRMS (EI^+): m/z calcd for $[C_9H_8N_2O_3]^+$: 193.0613, found 193.0616.

2-(5-Methoxy-2-nitrophenyl)propanenitrile (Table 2, Entry 23, **1w**)

Yellow oil (1.91g, 93%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 9.2 Hz, 1 H), 7.16 (d, J = 2.6 Hz, 1 H), 6.88 (dd, J = 9.2, 2.6 Hz, 1H), 4.85 (q, J = 7.0 Hz, 1 H), 3.87 (s, 3 H), 1.63 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 224.07, 164.08, 140.08, 135.45, 128.71, 120.92, 114.93, 113.77, 77.48, 77.16, 76.84, 56.21, 28.63, 21.12; HRMS (EI^+): m/z calcd for $[C_{10}H_{10}N_2O_3]^+$: 207.0770, found 207.0768.

2-(5-Methoxy-2-nitrophenyl)pentanenitrile (Table 2, Entry 24, **1x**)

Yellow solid (2.13g, 91%); m p. 63.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 9.2 Hz, 1 H), 7.14 (d, J = 2.6 Hz, 1 H), 6.87 (dd, J = 9.2, 2.6 Hz, 1 H), 4.83 (dd, J = 9.4, 4.8 Hz, 1 H), 3.87 (s, 3 H), 1.94-1.69 (m, 2 H), 1.66-1.45 (m, 2 H), 0.93 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.96, 140.21, 134.68, 128.76, 120.26, 115.34, 113.83, 77.48, 77.16, 76.84, 56.25, 37.48, 34.26, 20.85, 13.36; HRMS (EI^+): m/z calcd for $[C_{18}H_{23}N]^+$: 235.1083, found 235.1081.

2,2-Bis(2-nitrophenyl)acetonitrile (Table 2, Entry 26, **1z**)

Yellow solid (0.81g, 58%); m. p. 118 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14-8.09 (m, 2 H), 7.64 (m, 2 H), 7.56-7.49 (m, 4 H), 6.80 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.64, 134.47, 130.71, 130.37, 129.53, 126.42, 117.34, 77.41, 77.16, 76.91, 36.61; HRMS (EI^+): m/z calcd for $[C_{14}H_9N_3O_4]^+$: 284.0671, found 284.0675.

2-(1-Nitronaphthalen-2-yl)acetonitrile (Table 2, Entry 27, **1α**)

Yellow solid (1.29g, 61%); m. p. 120.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (d, J = 8.5 Hz, 1 H), 8.19 (d, J = 7.7 Hz, 1 H),

7.86–7.70 (m, 4 H), 4.36 (s, 2 H); ^{13}C NMR (100 MHz, DMSO–d_6) δ 146.45, 132.89, 132.42, 129.75, 128.47, 128.11, 126.47, 123.68, 121.71, 121.14, 117.41, 40.15, 39.94, 39.73, 39.52, 39.31, 39.10, 38.89, 19.95; HRMS (EI$^+$): m/z calcd for $[C_{12}H_8N_2O_2]^+$: 212.0586, found 212.0589.

2–(6–Methoxy–3–nitropyridin–2–yl)propanenitrile (Table 3, Entry 2, **3b**)

White solid (2.05g, 99%); m. p. 60.9 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, J = 9.0 Hz, 1 H), 6.76 (d, J = 9.0 Hz, 1 H), 4.91 (d, J = 7.1 Hz, 1 H), 4.03 (s, 3 H), 1.67 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.46, 150.86, 138.03, 136.67, 119.58, 111.59, 77.42, 77.16, 76.90, 55.08, 31.83, 18.69; HRMS (EI$^+$): m/z calcd for $[C_9H_9N_3O_3]^+$: 208.0722, found 208.0724.

2–(6–Methoxy–3–nitropyridin–2–yl)pentanenitrile (Table 3, Entry 3, **3c**)

Yellow liquid (1.34g, 57%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, J = 9.1 Hz, 1 H), 6.74 (d, J = 9.0 Hz, 1 H), 4.83 (dd, J = 9.2, 5.3 Hz, 1 H), 3.99 (s, 3 H), 2.00–1.82 (m, 2 H), 1.63–1.41 (m, 2 H), 0.90 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.07, 150.17, 138.04, 136.50, 118.53, 111.20, 54.80, 36.97, 34.92, 20.28, 12.99; HRMS (EI$^+$): m/z calcd for $[C_{11}H_{13}N_3O_3]^+$: 236.1035, found 236.1037.

Ethyl 3−cyano−3−(6−methoxy−3−nitropyridin−2−yl)propanoate (Table 3, Entry 4, **3d**)

White solid (1.42g, 51%); m. p. 81.3°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, J = 7.7 Hz, 1 H), 6.78 (d, J = 7.7 Hz, 1 H), 5.32−5.10 (m, 1 H), 4.04 (s, 2 H), 3.97 (s, 3 H), 3.29−3.18 (m, 1H), 3.05−2.92 (m, 1 H), 1.20−1.00 (m, 3 H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.95, 165.25, 147.81, 138.83, 136.71, 117.57, 111.85, 61.23, 54.90, 35.68, 32.45, 13.84; HRMS (EI^+): m/z calcd for $[C_{12}H_{13}N_3O_5]^+$: 280.0933, found 280.0932; IR (neat): 1735cm^{-1}.

5−Bromo−1*H*−indole (Table 1)

Brown solid (33.33mg, 68%); m. p. 37 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.69 (s, 1H), 7.21−7.16 (m, 2H), 7.12 (s, 1H), 6.42 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.51, 129.75, 125.49, 124.97, 123.36, 113.15, 112.55, 102.46, 77.48, 77.16, 76.84; HRMS (EI^+): m/z calcd for $[C_8H_6BrN]^+$: 194.9684, found 194.9683.

1*H*−Indole (Table 2, Entry 1, **2a**)

White solid (19.92mg, 68%); m. p. 51 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (s, 1 H), 7.55 (d, J = 7.7 Hz, 1 H), 7.18 (d, J = 7.8 Hz, 1 H), 7.12−7.06 (m, 1 H), 7.02 (t, J = 7.3 Hz, 1 H), 6.95 (s, 1 H), 6.43

(s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.81, 127.88, 124.31, 122.02, 120.79, 119.88, 111.17, 102.53, 77.42, 77.16, 76.91; HRMS (EI^+): m/z calcd for $[C_8H_7N]^+$: 117.0578, found 117.0579.

3-Methyl-1*H*-Indole (Table 2, Entry 2, **2b**)

Yellow solid (26.23mg, 80%); m. p. 97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1 H), 7.51 (d, J = 7.8 Hz, 1 H), 7.23 (d, J = 8.0 Hz, 1 H), 7.13-7.08 (m, 1 H), 7.04 (t, J = 8.0 Hz, 1 H), 6.85 (s, 1 H), 2.26 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.35, 128.38, 121.97, 121.69, 119.22, 118.94, 111.80, 111.06, 77.48, 77.16, 76.84, 9.79; HRMS (EI^+): m/z calcd for $[C_9H_9N]^+$: 131.0735, found 131.0734.

3-Ethyl-1*H*-Indole (Table 2, Entry 3, **2c**)

Yellow solid (28.17mg, 97%); m. p. 36 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (s, 1 H), 7.53 (d, J = 7.9 Hz, 1 H), 7.24 (d, J = 8.1 Hz, 1 H), 7.10 (t, J = 7.5 Hz, 1 H), 7.03 (t, J = 7.4 Hz, 1 H), 6.86 (s, 1 H), 2.71 (q, J = 7.5 Hz, 2 H), 1.25 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.53, 127.55, 121.99, 120.55, 119.17, 119.06, 118.93, 111.15, 77.41, 77.16, 76.91, 18.47, 14.59; HRMS (EI^+): m/z calcd for $[C_{10}H_{11}N]^+$: 145.0891, found 145.0892.

3-Propyl-1*H*-Indole (Table 2, Entry 4, **2d**)

Brown oil (32.24mg, 81%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1 H), 7.53 (d, J = 7.8 Hz, 1 H), 7.22 (d, J = 8.1 Hz, 1 H), 7.12−7.07 (m, 1 H), 7.02 (m, 1 H), 6.83 (s, 1 H), 2.65 (t, J = 7.5 Hz, 2 H), 1.70−1.60 (m, 2 H), 0.91 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.44, 127.76, 121.90, 121.24, 119.14, 117.04, 111.14, 77.48, 77.16, 76.84, 27.41, 23.46, 14.32; HRMS (EI^+): m/z calcd for $[C_{11}H_{13}N]^+$: 159.1048, found 159.1046.

3−Phenyl−1*H*−indole (Table 2, Entry 5, **2e**)

Yellow solid (40.10mg, 83%); m. p. 86 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (s, 1 H), 7.86 (d, J = 7.9 Hz, 1 H), 7.58 (d, J = 7.2 Hz, 2 H), 7.36 (m, 2 H), 7.29 (d, J = 8.1 Hz, 1 H), 7.21 (s, 2 H), 7.16 (m, 1 H), 7.11 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.76, 135.67, 128.90, 127.60, 126.11, 125.84, 122.52, 121.92, 120.44, 119.93, 118.40, 111.54, 77.41, 77.16, 76.91; HRMS (EI^+): m/z calcd for $[C_{14}H_{11}N]^+$: 193.0891, found 193.0893.

3−(4−Fluorophenyl)−1*H*−indole (Table 2, Entry 6, **2f**)

Brown solid (45.42mg, 86%); m. p. 94 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 1 H), 7.78 (d, J = 7.9 Hz, 1 H), 7.50 (m, 2 H), 7.29 (d, J = 8.1 Hz, 1 H), 7.15 (m, 2H), 7.11 (d, J = 7.6 Hz, 1 H), 7.03 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.58, 160.63, 136.69, 131.66, 129.07, 129.01, 125.82, 122.63, 121.72, 120.52, 119.64, 117.53, 115.80, 115.63, 111.58, 77.41, 77.16, 76.91; ^{19}F

NMR (376 MHz, $CDCl_3$) δ −116.99; HRMS (EI^+): m/z calcd for $[C_{14}H_{10}FN]^+$: 211.0797, found 211.0795.

3−(4−Chlorophenyl)−1*H*−indole (Table 2, Entry 7, **2g**)

Brown solid (40.41mg, 71%); m. p. 134 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.13 (s, 1 H), 7.80 (d, J = 7.9 Hz, 1 H), 7.51 (d, J = 8.4 Hz, 2 H), 7.33 (m, 3 H), 7.24 (m, 1 H), 7.18 (m, 1 H), 7.12 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.71, 134.14, 131.67, 129.00, 128.69, 125.58, 122.70, 122.02, 120.64, 119.65, 117.22, 111.64, 77.41, 77.16, 76.91; HRMS (EI^+): m/z calcd for $[C_{14}H_{10}ClN]^+$: 227.0502, found 227.0500.

3−(4−Methoxyphenyl)−1*H*−indole (Table 2, Entry 8, **2h**)

Brown solid (43.54mg, 78%); m. p. 127 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1 H), 7.82 (d, J = 7.8 Hz, 1 H), 7.51 (d, J = 8.3 Hz, 2 H), 7.31 (d, J = 8.0 Hz, 1 H), 7.16 (m, 2 H), 7.10 (m, 1H), 6.92 (d, J = 8.3 Hz, 2 H), 3.77 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.19, 136.68, 128.74, 128.23, 125.99, 122.42, 121.29, 120.26, 119.85, 118.09, 114.38, 111.48, 77.48, 77.16, 76.84, 55.48; HRMS (EI^+): m/z calcd for $[C_{15}H_{13}NO]^+$: 223.0997, found 223.0999.

3−Benzyl−1*H*−indole (Table 2, Entry 9, **2i**)

Brown solid (13.99mg, 27%; 25.39mg, 49% for 48 h); m. p. 104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.44 (d, J = 7.1 Hz, 1H), 7.25 (d, J = 6.5 Hz, 1H), 7.20 (s, 3H), 7.14 (s, 1H), 7.11 (d, J = 5.0 Hz, 2H), 7.01 (d, J = 7.1 Hz, 1H), 6.80 (s, 1H), 4.03 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.32, 136.55, 128.81, 128.45, 127.57, 126.00, 122.45, 122.16, 119.48, 119.27, 115.94, 111.19, 77.48, 77.16, 76.84, 31.72; HRMS (EI^+): m/z calcd for $[C_{15}H_{13}N]^+$: 207.1048, found 207.1049.

1*H*–Indole (Table 2, Entry 10, **2j**)

White solid (16.38mg, 56%); m. p. 51 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.12 (d, J = 7.9 Hz, 1H), 6.85 (d, J = 8.1 Hz, 1H), 6.71–6.66 (m, 1H), 6.65 (s, 1H), 6.59 (t, J = 7.0 Hz, 1H), 6.03 (s, 1H); ^{13}C NMR (101 MHz, cdcl$_3$) δ 135.88, 127.96, 124.24, 122.11, 120.85, 119.93, 111.14, 102.74, 77.48, 77.16, 76.84; HRMS (EI^+): m/z calcd for $[C_8H_7N]^+$: 117.0578, found 117.0579.

5–Fluoro–1*H*–indole (Table 2, Entry 11, **2k**)

Brown solid (23.99mg, 71%); m. p. 42 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1 H), 7.21 (m, 1 H), 7.19 (m, 1 H), 7.13 (m, 1 H), 6.86 (m, 1 H), 6.44–6.40 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.02, 157.15, 132.43, 128.27, 126.03, 111.73, 111.66, 110.62, 110.41, 105.63, 105.45, 102.92, 102.89, 77.41, 77.16, 76.91; ^{19}F NMR (376 MHz, $CDCl_3$) δ −124.95, −124.96, −124.97, −124.99, −

125.00, −125.01; HRMS (EI$^+$): m/z calcd for $[C_8H_6FN]^+$: 135.0484, found 135.0486.

5−Chloro−1*H*−indole (Table 2, Entry 12, 2l)

Brown solid (27.67mg, 73%); m. p. 65 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (s, 1 H), 7.64 (s, 1 H), 7.32 (d, J = 8.6 Hz, 1 H), 7.24 (m, 1 H), 7.18 (m, 1 H), 6.53 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.25, 129.07, 125.65, 125.58, 122.43, 120.23, 112.11, 102.52, 77.41, 77.16, 76.91; HRMS (EI$^+$): m/z calcd for $[C_8H_6ClN]^+$: 151.0189, found 151.0188.

5−Chloro−3−methyl−1*H*−indole (Table 2, Entry 13, **2m**)

Brown solid (31.47mg, 76%); m. p. 50 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 1 H), 7.45 (d, J = 1.7 Hz, 1 H), 7.13 (d, J = 8.6 Hz, 1 H), 7.04 (dd, J = 8.6, 2.0 Hz, 1 H), 6.87 (s, 1 H), 2.20 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.68, 129.54, 124.97, 123.14, 122.21, 118.51, 112.05, 111.65, 77.41, 77.16, 76.90, 9.65; HRMS (EI$^+$): m/z calcd for $[C_9H_8ClN]^+$: 165.0345, found 165.0343.

5−Chloro−3−propyl−1*H*−indole (Table 2, Entry 14, **2n**)

Brown oil (43.09mg, 89%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (s, 1 H), 7.48 (d, J = 1.5 Hz, 1 H), 7.14 (d, J = 8.6 Hz, 1 H), 7.03 (dd, J

= 8.6, 1.9 Hz, 1 H), 6.88 (s, 1 H), 2.59 (t, *J* = 7.5 Hz, 2 H), 1.66–1.58 (m, 2 H), 0.90 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.77, 128.92, 124.91, 122.68, 122.16, 118.67, 116.90, 112.11, 77.41, 77.16, 76.91, 27.23, 23.39, 14.23; HRMS (EI^+): m/z calcd for $[C_{11}H_{12}ClN]^+$: 193.0658, found 193.0659.

6–Chloro–1*H*–indole (Table 2, Entry 15, **2o**)

Brown solid (26.91mg, 71%); m. p. 78 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (s, 1 H), 7.56 (d, *J* = 8.4 Hz, 1 H), 7.37 (s, 1 H), 7.20–7.16 (m, 1 H), 7.12 (d, *J* = 8.4 Hz, 1 H), 6.55 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.23, 127.96, 126.55, 124.97, 121.66, 120.69, 111.08, 102.88, 77.41, 77.16, 76.90; HRMS (EI^+): m/z calcd for $[C_8H_6ClN]^+$: 151.0189, found 151.0187.

Ethyl 6–chloro–1H–indole–3–carboxylate (Table 2, Entry 16, **2p**)

White solid (50.88mg, 91%); m. p. 161°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.84 (s, 1H), 7.35 (s, 1H), 7.16 (s, 1H), 4.32 (q, *J* = 6.8 Hz, 2H), 1.35 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.94, 136.54, 131.45, 129.32, 124.56, 122.93, 122.73, 111.57, 109.62, 77.41, 77.16, 76.91, 60.14, 14.69; HRMS (EI^+): m/z calcd for $[C_{11}H_{10}ClNO_2]^+$: 223.0400, found 223.0402; IR (neat): 1667cm^{-1}.

5−Bromo−3−methyl−1*H*−indole (Table 2, Entry 17, **2q**)

Brown solid (40.96mg, 78%); m. p. 76 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 1 H), 7.61 (s, 1 H), 7.17 (d, J = 8.5 Hz, 1 H), 7.09 (d, J = 8.5 Hz, 1 H), 6.85 (s, 1 H), 2.19 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.94, 130.21, 124.74, 122.97, 121.63, 112.50, 111.57, 77.41, 77.16, 76.91, 9.65; HRMS (EI^+): m/z calcd for $[C_9H_8BrN]^+$: 208.9840, found 208.9837.

5−Bromo−3−propyl−1*H*−indole (Table 2, Entry 18, **2r**)

Brown oil (31.55mg, 53%); ^{1}H NMR (500 MHz, CDCl3) δ 7.80 (s, 1 H), 7.64 (s, 1 H), 7.16 (d, J = 8.6 Hz, 1 H), 7.10 (d, J = 8.6 Hz, 1 H), 6.86 (s, 1 H), 2.58 (t, J = 7.5 Hz, 2 H), 1.66−1.57 (m, 2 H), 0.90 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.04, 129.59, 124.69, 122.50, 121.77, 119.16, 116.83, 112.57, 112.46, 77.41, 77.16, 76.91, 27.22, 23.39, 14.23; HRMS (EI^+): m/z calcd for $[C_{11}H_{12}BrN]^+$: 237.0153, found 237.0151.

Ethyl 6−bromo−1*H*−indole−3−carboxylate (Table 2, Entry 19, **2s**)

White solid (61.66mg, 92%); m. p. 105°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1 H), 7.97 (d, J = 8.5 Hz, 1 H), 7.81 (d, J = 2.6 Hz, 1 H), 7.50 (s, 1 H), 7.30 (d, J = 8.5 Hz, 1 H), 4.32 (q, J = 7.1 Hz, 2 H), 1.35 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.11, 136.99, 131.52, 125.48, 124.85, 122.99, 116.85, 114.65,

109.46, 77.48, 77.16, 76.84, 60.20, 14.67; HRMS (EI^+): m/z calcd for $[C_{11}H_{10}BrNO_2]^+$: 266.9895, found 266.9892; IR (neat): 1666cm^{-1}.

5-(Trifluoromethyl)-1*H*-indole (Table 2, Entry 20, **2t**)

Brown solid (22.68mg, 49%); m. p. 67 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 1 H), 7.86 (s, 1 H), 7.35 (m, 2 H), 7.20 (m, 1H), 6.56-6.54 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.22, 127.34, 125.97, 118.91, 118.88, 118.65, 118.62, 111.40, 103.73, 77.41, 77.16, 76.91; ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.27; HRMS (EI^+): m/z calcd for $[C_9H_6F_3N]^+$: 185.0452, found 185.0451.

6-(Trifluoromethyl)-1*H*-indole (Table 2, Entry 21, **2u**)

Reddish brown solid (33.79mg, 73%); m. p. 103 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.21 (s, 1 H), 7.63 (d, J = 8.3 Hz, 1 H), 7.56 (s, 1 H), 7.27 (d, J = 8.3 Hz, 1 H), 7.23 (m, 1 H), 6.52 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.75, 130.34, 126.96, 121.23, 116.66, 116.64, 108.74, 108.71, 103.10, 77.41, 77.16, 76.91; ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.54; HRMS (EI^+): m/z calcd for $[C_9H_6F_3N]^+$: 185.0452, found 185.0450.

5-(Trifluoromethyl)-1*H*-indole (Table 2, Entry 22, **2v**)

Brown oil (25.02mg, 68%); m. p. 51 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (s, 1 H), 7.18 (d, J = 8.8 Hz, 1 H), 7.08 (m, 1 H), 7.03 (d, J = 2.4 Hz, 1 H), 6.78 (dd, J = 8.8, 2.5 Hz, 1 H), 6.40 (s, 1 H), 3.77 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.31, 131.09, 128.41, 124.99, 112.46, 111.83, 102.49, 102.46, 77.41, 77.16, 76.91, 55.99; HRMS (EI^+): m/z calcd for $[C_9H_9NO]^+$: 147.0684, found 147.0684.

5-Methoxy-3-methyl-1*H*-indole (Table 2, Entry 23, **2w**)

Brown solid (36.27mg, 90%); m. p. 62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1 H), 7.11 (d, J = 8.8 Hz, 1 H), 6.93 (s, 1 H), 6.83 (s, 1 H), 6.77 (d, J = 8.7 Hz, 1 H), 3.79 (s, 3 H), 2.22 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.95, 131.54, 128.71, 122.62, 112.15, 111.81, 111.47, 100.78, 77.48, 77.16, 76.84, 56.05, 9.84; HRMS (EI^+): m/z calcd for $[C_{10}H_{11}NO]^+$: 161.0841, found 161.0838.

5-Methoxy-3-propyl-1*H*-indole (Table 2, Entry 24, **2x**)

Brown oil (34.54mg, 73%); m. p. 50 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (s, 1 H), 7.26 (m, 1 H), 7.09 (s, 1 H), 6.97 (s, 1 H), 6.89 (m, 1 H), 3.91 (s, 3 H), 2.73 (t, J = 7.6 Hz, 2 H), 1.81-1.72 (m, 2 H), 1.04 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.87, 131.66, 128.13, 122.15, 116.76, 112.02, 111.83, 101.11, 77.41, 77.16, 76.91, 56.10, 27.44, 23.30, 14.32; HRMS (EI^+): m/z calcd for $[C_{12}H_{15}NO]^+$: 189.1154, found 189.1153.

5,6−Dimethoxy−1*H*−indole (Table 2, Entry 25, **2y**)

Dark brown solid (26.14mg, 59%); m. p. 152 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1 H), 7.01 (s, 1 H), 6.97 (s, 1 H), 6.76 (s, 1 H), 6.36 (s, 1 H), 3.83 (s, 3 H), 3.79 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.08, 145.18, 130.23, 122.87, 120.64, 102.39, 102.30, 94.58, 77.41, 77.16, 76.91, 56.39, 56.23; HRMS (EI^+): m/z calcd for $[C_{10}H_{11}NO_2]^+$: 177.0790, found 177.0791.

2−(1*H*−indol−3−yl)aniline (Table 2, Entry 26, **2z**)

Brown oil (41.13mg, 79%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (s, 1 H), 7.53 (m, 1 H), 7.28 (m, 1 H), 7.22 (m, 1 H), 7.19−7.12 (m, 2 H), 7.07 (m, 2 H), 6.74 (m, 2 H), 3.73 (s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.78, 136.27, 131.37, 128.06, 126.54, 123.11, 122.52, 120.63, 120.35, 120.12, 118.50, 115.51, 114.77, 111.47, 77.41, 77.16, 76.91; HRMS (EI^+): m/z calcd for $[C_{14}H_{12}N_2]^+$: 208.1000, found 208.0997.

1*H*−benzo[g]indole (Table 2, Entry 27, **2*α***)

Brown solid (32.19mg, 77%); m. p. 168 °C; ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.65 (s, 1 H), 7.84 (d, J = 8.1 Hz, 1 H), 7.80 (d, J = 8.1 Hz, 1 H), 7.64 (d, J = 8.6 Hz, 1 H), 7.43 (d, J = 8.8 Hz, 1 H), 7.40 (d, J = 7.3 Hz, 1 H), 7.34 (m, 1 H), 7.09 (m, 1 H), 6.62−6.57 (m, 1

H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 130.52, 129.00, 125.57, 123.98, 123.92, 122.38, 121.86, 120.94, 120.84, 119.46, 104.37, 77.41, 77.16, 76.91; HRMS (EI^+): m/z calcd for $[C_{12}H_9N]^+$: 167.0735, found 167.0738.

5-Methoxy-1*H*-pyrrolo[3,2-b]pyridine (Table 3, Entry 1, **4a**)

White solid (22.59mg, 61%); m. p. 99 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (s, 1 H), 7.50 (d, J = 8.7 Hz, 1 H), 7.24 (m, 1 H), 6.54 (d, J = 8.7 Hz, 1 H), 6.51 (s, 1 H), 3.93 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.39, 142.81, 126.70, 124.51, 122.09, 105.87, 102.68, 77.42, 77.16, 76.91, 53.54; HRMS (EI^+): m/z calcd for $[C_9H_{10}N_2O]^+$: 148.0637, found 148.0634.

5-methoxy-3-methyl-1*H*-pyrrolo[3,2-b]pyridine (Table 3, Entry 2, **4b**)

White solid (29.19mg, 72%); m. p. 88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1 H), 7.36 (d, J = 8.6 Hz, 1 H), 6.97 (s, 1 H), 6.48 (d, J = 8.6 Hz, 1 H), 3.92 (s, 3 H), 2.24 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.86, 142.34, 124.87, 124.64, 121.76, 111.66, 104.86, 77.48, 77.16, 76.84, 53.48, 8.67; HRMS (EI^+): m/z calcd for $[C_9H_{10}N_2O]^+$: 162.0793, found 162.0790.

5−methoxy−3−propyl−1*H*−pyrrolo[3,2−b]pyridine (Table 3, Entry 3, **4c**)

White solid (31.87mg, 67%); m. p. 55 °C; ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.44−7.40 (m, 1H), 7.00 (s, 1H), 6.50 (dd, J = 8.7, 1.8 Hz, 1H), 3.92 (s, 3H), 2.69 (t, J = 7.5 Hz, 2H), 1.75−1.67 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.70, 142.12, 124.88, 123.87, 121.52, 117.25, 105.08, 77.41, 77.16, 76.91, 53.34, 26.29, 23.15, 14.32; HRMS (EI^+): m/z calcd for $[C_{11}H_{14}N_2O]^+$: 190.1106, found 190.1107.

Ethyl 2−(5−methoxy−1H−pyrrolo[3,2−b]pyridin−3−yl)acetate (Table 3, Entry 4, **4d**)

White solid (38.07mg, 65%); m. p. 50 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1 H), 7.34 (d, J = 8.7 Hz, 1 H), 7.12 (s, 1 H), 6.47 (d, J = 8.7 Hz, 1 H), 4.13 (q, J = 7.1 Hz, 2 H), 3.89 (s, 3 H), 3.76 (s, 2 H), 1.21 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.88, 159.99, 141.56, 125.46, 124.45, 121.83, 108.51, 105.51, 77.41, 77.16, 76.90, 6]0.87, 53.30, 29.64, 14.39; HRMS (EI^+): m/z calcd for $[C_{12}H_{14}N_2O_3]^+$: 234.1004, found 234.1003; IR (neat): 1727cm^{-1}.

2−(5−Methoxy−1*H*−indol−3−yl)aniline (Scheme 2, eq 1, **6a**)

Brown oil (38.72mg, 65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.22−7.17 (m, 1H), 7.12 (d, J = 8.8 Hz, 1H), 7.09−7.04 (m,

2H), 6.93 (d, J = 2.2 Hz, 1H), 6.79 (dd, J = 8.8, 2.3 Hz, 1H), 6.76–6.68 (m, 2H), 3.67 (s, 5H); ^{13}C NMR (100 MHz, cdcl$_3$) δ 154.41, 144.74, 131.35, 131.23, 127.99, 126.83, 123.88, 120.70, 118.43, 115.46, 114.39, 112.93, 112.25, 101.67, 77.48, 77.16, 76.84, 55.90; HRMS (EI$^+$): m/z calcd for $[C_{15}H_{14}N_2O]^+$: 238.1106, found 238.1104.

2–(1*H*–indol–3–yl)–4–methoxyaniline (Scheme 2, eq 1, **7a**)

Brown oil (12.51mg, 21%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.22 (s, 1H), 7.17 (t, J = 7.5 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 6.86 (s, 1H), 6.71 (s, 2H), 3.70 (s, 3H), 3.23 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.62, 138.44, 136.28, 126.49, 123.25, 123.18, 122.61, 121.89, 120.26, 116.77, 116.60, 114.84, 113.94, 111.50, 77.48, 77.16, 76.84, 55.92; HRMS (EI$^+$): m/z calcd for $[C_{15}H_{14}N_2O]^+$: 238.1106, found 238.1105.

4–Chloro–2–(1*H*–indol–3–yl)aniline (Scheme 2, eq 2, **7b**)

Brown oil (29.73mg, 49%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.49 (d, J = 7.0 Hz, 1H), 7.32–7.26 (m, 1H), 7.19–7.10 (m, 3H), 7.10–6.97 (m, 2H), 6.62 (dd, J = 8.4, 2.5 Hz, 1H), 3.71 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.41, 136.22, 130.70, 127.69, 126.11, 123.28, 122.78, 122.74, 122.14, 120.36, 120.11, 116.49,

113.69, 111.58, 77.48, 77.16, 76.84; HRMS (EI^+): m/z calcd for $[C_{14}H_{11}ClN_2]^+$: 242.0611, found 242.0612.

2-(5-Chloro-1*H*-indol-3-yl)aniline (Scheme 2, eq 2, **6b**)

Brown oil (13.35mg, 22%); ^1H NMR (400 MHz, $cdcl_3$) δ 8.26 (s, 1H), 7.52 (s, 1H), 7.28 (d, J = 10.1 Hz, 2H), 7.19 (d, J = 5.9 Hz, 2H), 7.12 (d, J = 7.9 Hz, 2H), 6.75 (d, J = 7.7 Hz, 2H), 3.78 (s, 2H); ^{13}C NMR (101 MHz, $cdcl_3$) δ 144.78, 134.66, 131.34, 128.41, 127.76, 126.03, 124.35, 123.00, 119.93, 119.74, 118.56, 115.56, 114.81, 112.44, 77.48, 77.16, 76.84; HRMS (EI^+): m/z calcd for $[C_{14}H_{11}ClN_2]^+$: 242.0611, found 242.0611.

Reference

(1). (a) Sundberg, R. J. Pyrroles and Their Benzo Derivatives: Synthesis and Applications. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 4, pp 313. (b) Gribble, G. W. In *Comprehensive Heterocyclic Chemistry* II; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon, Oxford, UK, 1996; Vol. 2, pp 207. (c) Sundberg, R. J. *Indoles*; Academic Press: London, 1996. (d) d' Ischia, M.; Napolitano, A.; Pezzella, A. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. S.; Taylor, R. J. K., Eds.; Elsevier: Oxford, UK, 2008; Vol. 3, pp 353. (e) Dandia, A.; Singh, R.; Khaturia, S.; Merienne, C.; Morgant, G.; Loupy, A. *Bioorg. Med. Chem.* 2006, *14*, 2409. (f) Suzen, S. *Top. Heterocycl. Chem.* 2007, *11*, 145. (g) Brancale, A.; Silvestri, R. *Med. Res. Rev.* 2007, *27*, 209. (h) de Sa Alves, F. R.; Barreiro, E. J.; Fraga, C. A. M. *Mini-Rev. Med. Chem.* 2009, *9*, 782.

(2) (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* 2005, *105*, 2873. (b) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* 2006, *106*, 2875. (c) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* 2007, *36*, 1173. (d) Bartoli, G.; Bencivenni, G.; Dalpozzo, R. *Chem. Soc. Rev.* 2010, *39*, 4449. (e) Cacchi, S.; Fabrizi, G. *Chem. Rev.* 2011, *111*, PR215. (f) Platon, M.; Amardeil, R.; Djakovitch, L.; Hierso, J.-C. *Chem. Soc. Rev.* 2012, *41*, 3929. (g) Lancianesi, S.; Palmieri, A.; Petrini, M.

Chem. Rev. 2014, *114*, 7108. (h) Dalpozzo, R. *Chem. Soc. Rev.* 2015, *44*, 742.

(3) (a) Wrobel, Z.; Makosza, M. *Synlett* 1993, 597. (b) Macor, J. E.; Wehner, J. M. *Heterocycles* 1993, *35*, 349.

(4) (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* 2005, *105*, 2873. (b) Jouclaa, L.; Djakovitcha, L. *Adv. Synth. Catal.* 2009, *351*, 673.

(5) (a) Stephen, H. *J. Chem. Soc. Trans.* 1925, *127*, 1874. (b) Macor, J. E.; Wehner, J. M. *Tetrahedron Lett.* 1991, *32*, 7195. (c) Belly, M.; Suaer, E.; Beaudoin, D.; Duspara, P.; Trimble, L. A.; Dubé, P. *Tetrahedron Lett.* 2006, *47*, 159. (d) Lee, S. J.; Fowler, J. S.; Alexoff, D.; Schueller, M.; Kim, D.; Nauth, A.; Weber, A.; Kim, S. W.; Hooker, J. M.; Ma, L.; Qu, W. *Org. Biomol. Chem.* 2015, *13*, 11235.

(6) Mąkosza, M.; Danikiewicz, W.; Wojciechowski, K. *Liebigs. Ann. Chem.* 1988, 203.

(7) Motoyama, Y.; Kamo, K.; Nagashima, H. *Org. Lett.,* 2009, *11*, 1345.

(8) (a) Sajiki, H.; Ikawa, T.; Hirota, K. *Org. Lett.* 2004, *6*, 4977. (b) Ikawa, T.; Fujita, Y.; Mizusaki, T.; Betsuin, S.; Takamatsu, H.; Maegawa, T.; Monguchi, Y.; Sajiki, H. *Org. Biomol. Chem.* 2012, *10*, 293. (c) Srimani, D.; Feller, M.; Ben-David, Y.; Milstein, D. *Chem. Commun.* 2012, 48, 11853.

(9) (a) Park, K. H.; Son, S. U.; Chung, Y. K. *Chem. Commun.* 2003, 1898. (b) Park, K. H.; Son, S. U.; Chung, Y. K. *Org. Lett.* 2002, *4*,

4361. (c) Yuan, H.; Yoo, W.-J.; Myamura, H.; Kobayashi, S. *J. Am. Chem. Soc.* 2012, *134*, 13970. (d) Yasukawa, T.; Miyamura, H.; Kobayashi, S. *J. Am. Chem. Soc.* 2012, *134*, 16963. (e) Udumula, V.; Tyler, J. H.; Davis, D. A.; Wang, H.; Linford, M. R.; Minson, P. S.; Michaelis, D. *J. ACS Catal.* 2015, *5*, 3457. (f) Sankar, M.; Dimitratos, N.; Miedziak, P. J.; Wells, P. P.; Kiely, C. J.; Hutchings, G. *J. Chem. Soc. Rev.* 2012, *41*, 8099.

(10) (a) Park, J. H.; Chung, Y. K. *Dalton Trans.* 2008, 2369. (b) Park, J. H.; Kim, S. Y.; Chung, Y. K. *Synlett* 2007, 453.

(11) (a) Park, J. H.; Kim, E.; Chung, Y. K. *Org. Lett.* 2008, *10*, 4719. (b) Park, J. W.; Chung, Y. K. *ACS Catal.* 2015, *5*, 4846.

(12) Lu, S.; Wang, J.; Cao, X.; Li, X.; Gu, H. *Chem. Commun.* 2014, *50*, 3512.

(13) (a) Srihan, P.; Padmabhavani, B.; Ramesh, S.; Kumar, Y. B.; Singh, A.; Ummanni, R. *Bioorg. Med. Chem. Lett.* 2015, *25*, 2360. (b) Patil, N. T.; Shinde, V. S.; Sridhar, B. *Angew. Chem. Int. Ed.*, 2013, *52*, 2251. (c) Singh, V.; Hutait, S.; Batra, S. *Eur. J. Org. Chem.*, 2009, 6211.

(14) (a) Mérour, J.-Y.; Buron, F.; Plé, K.; Bonnet, P.; Routier, S. *Molecules* 2014, *19*, 19935. (b) Zhihui, W.; Xiao, W. *Progress in Chem.* 2012, 1974. (c) Song, J. J.; Reeves, J. T.; Gallou, F.; Tan, Z.; Yee, N. K.; Senanayake, C. H. *Chem. Soc. Rev.* 2007, *36*, 1120. (d) Larraya, C.; Guillard, J.; Renard, P.; Audinot, V.; Boutin, J. A.; Delagrange, P.; Bennejean, C.; Viaud-Massuard, M.-C. *Eur. J. Med.*

Chem. 2004, *39*, 515.. (e) Filla, S. A.; Mathes, B. M.; Johnson, K. W.; Phebus, L. A.; Cohen, M. L.; Nelson, D. L.; Zgombick, J. M.; Erickson, J. A.; Schenck, K. W.; Wainscott, D. B.; Branchek, T. A.; Schaus, J. M. *J. Med. Chem.* 2003, *46*, 3060. (f) Mazeas, D.; Guillaumet, G.; Viaud, M.-C. *Heterocycles* 1999, 50, 1065.

(15) Park, J. H.; Kim, E.; Chung, Y. K. *Org. Lett.* 2008, 10, 4719.

(16) According to ICP-AES data of immobilized Co2Rh2/C heterobimetallic nanoparticles, 4 w % of Co2Rh2 (MW = 323.66) was fixed and the mol ratio of Co : Rh was 1.02 : 1. Thus, Co2Rh2/C heterobimetallic nanoparticle was stoichiometrically fixed to the charcoal support. As a result, 3.6 mg of Co2Rh2 in 90 mg of heterobimetallic nanoparticles used was corresponding to the 5 mol % of 0.25 mmol of reactants. See the following about determination of metal loading: Park. J. W.; Chung, Y. K. *ACS Catalysis*, 2015, 5, 4846.

(17) Schlosser; J.; Johannes, E.; Zindler, M.; Lemmerhirt, J.; Sommer, B.; Schütt, M.; Peifer, C., *Tetrahedron Lett.* 2015, 56, 89.

(18) Sharma, K.; Wolstenhulme, J. R.; Painter, P. P.; Yeo, D.; Grande-Carmona, F.; Johnston, C. P.; Tantillo, D. J.; Smith, M. D., *J. Am. Chem. Soc.* 2015, 137, 13414.

(19) Stazi, F.; Maton, W.; Castoldi, D.; Westerduin, P.; Curcuruto, O.; Bacchi, S., Synthesis *2010*, 19, 3332.

(20) Jeanty, M.; Suzenet, F.; Guillaumet, G., J. Org. Chem. *2008*, 73, 7390.

(21) Beesu, M.; Malladi, S. S.; Fox, L. M.; Jones, C. D.; Dixit, A.; David, S. A., *J. Med. Chem.*, **2014**, 57, 7325.

(22) Park, L.; Keum, G.; Kang, S. B.; Kim, K. S.; Kim, Y., *J. Chem. Soc., Perkin Trans. 1*, **2000**, 4462.

국문초록

코발트-로듐 불균일 촉매로 나이트로아릴아세토나이트릴의 환원적 고리화 반응을 통해 인돌을 합성하고 나이트로피리딜아세토나이트릴의 환원적 고리화반응을 통해 아자인돌을 합성하하는데 성공하였다. 이 반응은 1기압의 수소가스와 실온 (25℃)의 매우 온화한 조건에서도 다른 첨가물 없이 인돌을 합성하는 첫 번째 연구이다. 또한 이 반응은 그램-스케일에서도 합성이 가능함을 밝혀냈다. 이 촉매반응은 반응조건에서 매우 안정하여 10회 이상의 재사용에도 촉매 활성을 잃지 않았다.

주요어: 불균일 촉매반응, 수소화, 환원적 고리반응, 인돌, 아자인돌, 탠덤반응, 온화한 조건

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